18. (Amended) The method of claim 1 or 5, wherein the nucleic acid molecule is a purified nucleic acid molecule.

Please enter the following new claim:

21. (New) The method of claim 1 or 5, wherein the nucleic acid, when delivered, reduces development of choroidal neovascularization.

## ***REMARKS***

Claims 1-18 have been amended. Claims 19 and 20 have been cancelled without prejudice. Claim 21 has been added. Upon entry of this amendment, claims 1-18, and 21 will be pending in this application.

The outstanding Office Action was addressed to the Paul T. Clark at the firm of Clark and Elbing, LLP. Responsibility for the application has been transferred to the firm of Testa, Hurwitz, and Thibeault, LLP. Accordingly, please send all further communications to the Patent Administrator, Testa, Hurwitz & Thibeault, LLP, 125 High Street, Boston, MA 02110.

Support for the amendments to claims 1 and 5 may be found, for example, on page 13, lines 8 and 16-18, and Example 1 of the application, as filed. Support for the amendments to claims 8, 12 and 13 may be found, for example, in claims 8, 12 and 13, as filed. Claims 2-4, 6, 7, 11, 14, and 18 have been amended to clarify antecedent basis, and claims 9, 10, and 15-17 have been amended to modify grammar. Basis for new claim 21 may be found, for example, on page 34, lines 10-14 of the application as filed. Applicants believe that the amendments introduce no new matter.

Each of the issues raised in the Office Action are addressed below in the order in which they appear in the Office Action.

## ***Oath/Declaration***

According to page 2 of the Office Action, the oath or declaration reportedly is defective. Applicants enclose an executed Supplemental Declaration and Power of Attorney document, and submit that the Supplemental Declaration obviates this objection. Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

***Rejection of Claims 1-18 Under 35 U.S.C. §112, First Paragraph***

According to pages 3-8 of the outstanding Office Action, claims 1-18 presently stand rejected under 35 U.S.C. §112, first paragraph. The Office Action alleges that the specification fails to enable one skilled in the art to practice the claimed invention. Applicants respectfully traverse this rejection to the extent that it is maintained over the claims, as amended, for the following reasons.

The Office Action suggests that the specification fails to provide an enabling disclosure for the claimed method because the specification teaches that the only use for the method is gene therapy. Applicants disagree and submit that the claimed delivery method need not be used in combination with a gene therapy protocol. The gene transfer technology referred to on page 13 of the specification is just one of the exemplary uses of the claimed invention. Applicants submit that the claimed invention, as amended, is directed to a method of delivering a nucleic acid molecule into the interior of a mammalian eye. The method, according to claim 1 for example, comprises contacting a scleral (outer) surface of the eye with a nucleic acid molecule having a molecular weight no greater than 150 kDa such that the nucleic acid passes through the sclera and into the interior of the eye.

Contrary to the Office Action, Applicants submit that the claims are not necessarily "directed to methods of gene therapy." All that is required is that a particular nucleic acid traverse the sclera and enter the interior of the eye. Applicants submit that the specification provides a detailed discussion of the types and characteristics of molecules that can be delivered transclerally (see, for example, the first full paragraph on page 13 and Example 1). In addition, the specification provides a detailed description of how to apply such molecules to the outer surface of the eye for transfer through the sclera, and methods for actually detecting transfer of molecules of interest through the sclera (see, for example, the paragraph bridging pages 11 and 12, and Examples 1-5 and 8). Applicants submit that the description fully enables one skilled in the art to practice the claimed delivery method.

Moreover, Applicants submit that nucleic acid molecules need not be part of a gene therapy protocol in order to impart therapeutic benefit. In other words, the nucleic acid molecules need

not be targeted to, transferred into and/or expressed within a particular cell in order to provide a beneficial effect. Under certain circumstances, for example, when a nucleic acid exhibits an effect absent translation, all that is required is that the nucleic acid molecule traverse the sclera and enter the interior of the eye. For example, Applicants submit a copy of a poster co-authored by Anthony Adamis (a co-inventor of the claimed invention) and presented at the annual meeting of the Association for Research in Vision and Opthalmology in 2002 (identified as article C3 in the enclosed PTO-1449 form). The poster indicates that an exemplary nucleic acid molecule (an anti-Vascular Endothelial Growth Factor (VEGF) aptamer known as EYE001), when released from poly (lactic-co-glycolic) acid microspheres disposed on a scleral surface of a rabbit eye, can pass through the sclera (see, Table 1). Furthermore, the poster confirms that the nucleic acid molecule, when released from the microspheres, can still exhibit its biological effect (see, Figure 6). Applicants submit that the development of aptamers, for example, aptamers that bind VEGF was known in the art before January 5, 1999 (see, for example, U.S. Patent Nos. 5,475,096; 5,582,981; 5,756,291 and 5,840,867, and the scientific articles Ruckman *et al.* (1998) J. BIOL. CHEM. 273: 20556-20567 (identified as article C7 in the enclosed PTO-1449 form) and Jellinek *et al.* (1994) BIOCHEM. 33: 10450-10456 (identified as article C5 in the enclosed PTO-1449 form)).

In addition, Applicants enclose a copy of a paper (identified as article C4 in the enclosed PTO-1449 form), which describes a Phase 1A clinical trial using the anti-VEGF nucleic acid molecule. Applicants submit that the paper reports preliminary results of a phase 1A clinical study in which the anti-VEGF aptamer EYE001 was administered by intravitreal injection to fifteen patients with subfoveal choroidal neovascularization secondary to exudative age-related macular degeneration (AMD). The results of the phase 1A study indicated that 80% of the patients showed stable or improved vision three months after treatment, and that 27% of the eyes demonstrated at least a three-line improvement in vision on an Early Treatment for Diabetic Retinopathy Study chart.

Applicants submit that molecules that bind to an extracellular protein, for example, VEGF, need not enter cells to inhibit angiogenesis. Accordingly, like the antibodies in the specification, nucleic acid molecules can bind to and inhibit VEGF activity, and thus can act like other drugs

which exhibit a biological effect without having to target, enter into, and/or be expressed in a particular cell.

Furthermore, the Office Action indicates that the specification fails to describe how to "deliver agents across the sclera in the absence of an osmotic pump." Applicants submit that the specification (for example, in the paragraph bridging pages 11 and 12) describes a variety of devices (for example, an osmotic pump, a mechanical pump, or a microchip) for applying an agent onto the surface of the eye. Once applied, the agent can pass through the sclera into the interior of the eye. Applicants submit that the choice of such a device was within the level of skill in the art at the time the invention was made. Furthermore, Applicants believe that the objection relating to the delivery of agents greater than 150 kDa is rendered moot by the amendment to, for example, claim 1.

In view of the foregoing, Applicants respectfully submit that the specification fully enables the invention defined by the claims, as amended, and, therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

According to page 10 of the outstanding Office Action, claims 1-18 presently stand rejected under 35 U.S.C. §112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was in possession of the invention. Applicants respectfully traverse this rejection to the extent that it is maintained of the claims, as amended, for the following reasons.

Applicants submit that the claimed invention is directed to a method of delivering a nucleic acid molecule into a mammalian eye. The method, according to claim 1 for example, comprises contacting a scleral surface of the eye with a nucleic acid molecule having a molecular weight no greater than 150 kDa so that the nucleic acid can pass through the sclera into the interior of the eye. Applicants submit that such a method may work for a variety of nucleic acid molecules having the claimed features. Applicants respectfully submit that they were in possession of claimed method (see, for example, the paragraph bridging pages 6 and 7, the first full paragraphs of pages 9 and 13, and Example 1 of the application, as filed) and, therefore, respectfully request that the rejection be reconsidered and withdrawn.

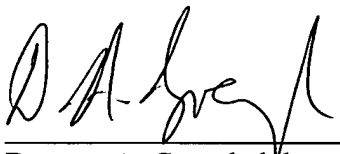
***Rejection of Claims 1-18 Under 35 U.S.C. §112, Second Paragraph***

According to pages 10 and 11 of the outstanding Office Action, claims 1-18 presently stand rejected for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse these rejections in view of the amendments to claims 1-18 and, therefore, respectfully request that these rejections be reconsidered and withdrawn.

***Conclusion***

In view of the foregoing amendments and remarks, Applicants respectfully submit that the case is in condition for immediate allowance. Early favorable action is respectfully solicited.

Respectfully submitted,



Date: November 20, 2002
Reg. No. 38,678

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## ***MARKED-UP COPY OF AMENDMENTS TO SPECIFICATION***

On page 1, immediately after the heading "Cross Reference to Related Applications" amend the paragraph starting with "This application" and ending with "1999." to read

-- This application [is a continuation-in-part of U.S.S.N.] claims the benefit of U.S. Provisional Application Serial No. 60/114,905, filed January 5, 1999. --

## ***MARKED-UP COPY OF AMENDMENTS TO CLAIMS***

Please amend claims 1-18 as follows:

1. (Amended) A method [for the targeted unidirectional delivery of a therapeutic or diagnostic agent to the eye of a mammal] of delivering a nucleic acid molecule into a mammalian eye, [said] the method comprising contacting [the sclera of said mammal with said therapeutic or diagnostic agent together with means for facilitating the transport of said agent through the sclera] a scleral surface of the eye with a nucleic acid molecule having a molecular weight no greater than 150 kDa such that the nucleic acid passes through the sclera and into the interior of the eye.

2. (Amended) The method of claim 1, wherein the nucleic acid [A method for the targeted unidirectional delivery of a therapeutic or diagnostic agent to the eye of a mammal, said method comprising contacting the sclera of said mammal with said therapeutic or diagnostic agent, wherein said agent] has a molecular weight of at least 70 kDa.

3. (Amended) The method of claim 2, wherein [said therapeutic or diagnostic agent] the nucleic acid has a molecular weight of at least 100 kDa.

4. (Amended) The method of claim 3, wherein [said therapeutic or diagnostic agent] the nucleic acid has a molecular weight of at least 120 kDa.

5. (Amended) A method [for the targeted unidirectional delivery of a therapeutic or diagnostic agent to the eye of a mammal] of delivering a nucleic acid molecule into a mammalian eye, [said] the method comprising contacting [the sclera of said mammal with said therapeutic or diagnostic agent, wherein said agent has a molecular radius of at least 0.5 nm] a scleral surface of the eye with a nucleic acid molecule having a molecular radius of at least 0.5 nm so that the nucleic acid passes through the sclera and into the interior of the eye.

6. (Amended) The method of claim 5, wherein [said therapeutic or diagnostic agent] the nucleic acid has a molecular radius of at least 3.2 nm.

7. (Amended) The method of claim 5, wherein [said therapeutic or diagnostic agent] the nucleic acid has a molecular radius of at least 6.4 nm.

8. (Amended) The method of claim 1[, 2,] or 5, [wherein, prior to contacting said sclera with said agent, said sclera is treated to thin it] comprising the additional step of thinning the sclera prior to contacting the scleral surface with the nucleic acid.

9. (Amended) The method of claim 8, wherein [said] the sclera has a thickness less than 70% of its pre-thinned thickness.

10. (Amended) The method of claim 9, wherein [said] the sclera has a thickness less than 60% of its pre-thinned thickness.

11. (Amended) The method of claim 1 [2] or 5, wherein the nucleic acid [said therapeutic or diagnostic agent] is contacted with said sclera together with means for facilitating the transport of [said agent] the nucleic acid through the sclera.

12. (Amended) The method of claim 1[, 2] or 5, wherein the nucleic acid is delivered to the sclera by a pump [said device is an osmotic, mechanical, or solid state transport facilitating device, or a polymer].

13. (Amended) The method of claim 12, wherein [said device is a pump] the pump is a mechanical or osmotic pump.

14. (Amended) The method of claim 1 or 5 [12], wherein [said device comprises] the nucleic acid is delivered to by sclera by a microchip.

15. (Amended) The method of claim 1[, 2,] or 5, wherein [said] the mammal is a human.

16. (Amended) The method of claim 1[, 2,] or 5, wherein [said] the method is used to treat a retinal or choroidal disease.

17. (Amended) The method of claim 16, wherein [said] the retinal or choroidal disease is selected from the group consisting of macular degeneration, diabetic retinopathy, retinitis

pigmentosa and other retinal degenerations, retinal vein occlusions, sickle cell retinopathy, glaucoma, choroidal neovascularization, retinal neovascularization, retinal edema, retinal[,] ischemia, proliferative vitreoretinopathy, and retinopathy of prematurity.

18. (Amended) The method of claim 1[, 2,] or 5, wherein [said therapeutic agent is selected from the group consisting of purified polypeptides,] the nucleic acid molecule is a purified nucleic acid molecule[s, synthetic organic molecules, and naturally occurring organic molecules].